

VISIT...

LANZAROTE
Caliente.COM

Short communication

Ibogaine-like effects of noribogaine in ratsS.D. Glick^{*}, S.M. Pearl, J. Cai, I.M. Maisonneuve*Department of Pharmacology and Neuroscience, Albany Medical College, New Scotland Avenue, Albany, NY 12208, USA*

Accepted 12 December 1995

Abstract

Ibogaine is a naturally occurring alkaloid that has been claimed to be effective in treating addiction to opioids and stimulants; a single dose is claimed to be effective for 6 months. Analogously, studies in rats have demonstrated prolonged (one or more days) effects of ibogaine on morphine and cocaine self-administration even though ibogaine is mostly eliminated from the body in several hours. These observations have suggested that a metabolite may mediate some of the effects of ibogaine. Recently, noribogaine was identified as a metabolite of ibogaine. Accordingly, the present study sought to determine, in rats, whether noribogaine had pharmacological effects mimicking those of ibogaine. Noribogaine (40 mg/kg) was found to decrease morphine and cocaine self-administration, reduce the locomotor stimulant effect of morphine, and decrease extracellular levels of dopamine in the nucleus accumbens and striatum. All of these effects were similar to effects previously observed with ibogaine (40 mg/kg); however, noribogaine did not induce any ibogaine-like tremors. The results suggest that noribogaine may be a mediator of ibogaine's putative anti-addictive effects.

Keywords: Ibogaine; Noribogaine; Morphine; Cocaine; Drug self-administration; Microdialysis; Dopamine

Ibogaine, an alkaloid found in the root bark of the African shrub *Tabernanthe iboga*, has been claimed to be effective in treating both opiate (heroin) addiction and stimulant (cocaine and amphetamine) abuse (U.S. patents No. 4,499,096, Feb. 12, 1985 and No. 4,587,243, May 6, 1986, respectively). Ibogaine treatment is said to interrupt the 'physiological and psychological aspects' of addiction and to greatly reduce or abolish the desire to use drugs. In both opiate and stimulant syndromes, a single oral treatment of ibogaine (6 to 19 mg/kg) is said to be effective for about six months; a series of four treatments is claimed to be efficacious for approximately three years. Using an animal (rat) model of drug addiction, we sought to determine whether these claims could be substantiated under controlled conditions. In our initial study [4], ibogaine dose-dependently decreased morphine self-administration in the hour after ibogaine treatment (acute effect) and, to a lesser but significant extent, a day later (aftereffect). In some rats there was a persistent decrease in morphine intake for several days or weeks after a single injection of ibogaine whereas other rats began to show such persistent

changes after two or three weekly injections. We [2] and others [1] subsequently observed similar effects of ibogaine on cocaine self-administration in rats.

The basis for the long-term effects of ibogaine has been the subject of considerable conjecture. We initially postulated that ibogaine might have an active and persistent metabolite [4,5]. Recent evidence has supported this idea. Noribogaine, which is probably ibogaine's primary metabolite [6], appears to persist in plasma for a prolonged period of time (i.e. at least 24 h) and has several biochemical actions shared by ibogaine, including binding to kappa opioid [9] and NMDA [7] receptors. Using rats, we now report that noribogaine, like ibogaine, decreases morphine and cocaine self-administration, antagonizes the motor stimulant effect of morphine, and decreases extracellular levels of dopamine in the nucleus accumbens and striatum.

Noribogaine hydrochloride was provided by NIDA; the dose used in all experiments was 40 mg/kg, administered intraperitoneally. All subjects were naive female Sprague–Dawley (Taconic, Germantown, NY) rats approximately 3 months old and weighing 230–250 g at the beginning of an experiment.

The intravenous self-administration procedure has been described previously (e.g. [2,4]). Briefly, responses on either of two levers (mounted 15 cm apart on the front wall of each operant test cage) were recorded on an IBM compatible 386 computer with a Med Associates, Inc.

^{*} Corresponding author. Department of Pharmacology and Neuroscience (A-136), Albany Medical College, Albany, NY 12208, USA. Fax: (1) (518) 262-5799.

interface. The intravenous self-administration system consisted of polyethylene-silicone cannulas constructed according to the design of Weeks [11], BRS/LVE harnesses and commutators, and Harvard Apparatus infusion pumps (#55-2222). Shaping of the bar-press response was initially accomplished by training rats to bar-press for water. Cannulas were then implanted in the external jugular vein according to procedures described by Weeks [11]. Self-administration testing began with a single 24-h session followed by daily 1-h sessions, 5 days (Monday–Friday) a week. Depending upon the group, a lever-press response produced either a 20 μ l (morphine) or 50 μ l (cocaine) infusion of drug solution (0.01 mg of morphine sulfate or 0.1 mg of cocaine hydrochloride) in about 0.4 (morphine) or 1.0 (cocaine) second. Since all rats generally weighed 250 ± 20 g, each response delivered approximately 0.04 mg/kg of morphine or 0.4 mg/kg of cocaine. Experiments to assess the effects of noribogaine were begun when baseline self-administration rates stabilized ($\leq 10\%$ variation from 1 day to the next across 5 days), usually after 2 weeks of testing. Noribogaine or saline was administered to different groups of rats responding for morphine or saline; injections were made on Wednesdays, fifteen minutes before a self-administration session. In order to provide an indication of the specificity of noribogaine's effects on bar-pressing for morphine and cocaine, noribogaine was also administered to other rats bar-pressing for water on a comparable schedule (continuous reinforcement; 1-h sessions).

The effect of noribogaine on morphine-induced locomotor stimulation was studied using the same procedures employed with ibogaine [10]. Locomotor activity was assessed using cylindrical photocell activity cages (60 cm, three crossing beams) interfaced to an IBM compatible 386 computer. Different groups of rats were pretreated with noribogaine or saline, and 19 h later, treated with morphine sulfate (5 mg/kg, i.p.) immediately before being placed into the activity cages. Locomotor activity was monitored for 3 h thereafter.

The microdialysis procedures used to assess the effects of noribogaine on extracellular levels of dopamine and its metabolites in the nucleus accumbens and striatum have been used extensively in this laboratory (e.g. [2,5]). Briefly, under pentobarbital anesthesia, rats were implanted stereotactically with guide cannulas over the nucleus accumbens and striatum so that, when inserted, the tips of the dialysis probes would be located in the shell of the nucleus accumbens (rostral, +1.6 mm from bregma; lateral, ± 0.7 mm; ventral, –8.6 mm from the skull surface) and in the striatum (rostral, +0.5 mm; lateral, ± 2.9 mm; ventral, –7.0 mm) [8]. The two cannulas were fixed firmly in the skull with dental cement. One cannula was implanted in the left side of the brain, and the other in the right side of the brain; the side (left or right) assigned to each region (nucleus accumbens or striatum) was alternated from animal to animal.

At least 4 days after surgery, a rat was placed in a dialysis chamber, a cylindrical (30 cm diameter) Plexiglas cage providing free access to food and water. Probes (2 or 3 mm, respectively, for nucleus accumbens or striatum; CMA 8309562 or CMA8309563) were then lowered into the guide cannulas. The dialysis probes were continuously perfused with a solution containing 146 mM NaCl, 2.7 mM KCl, 1.2 mM CaCl_2 and 1.0 mM MgCl_2 at a flow rate of 1 μ l/min. On the next morning (15–20 h later), the dialysis experiment was carried out on a freely moving animal. Twenty-min fractions were collected in vials containing 2 μ l of 1.1 N perchloric acid solution (containing 5 mg/l EDTA and 5 mg/l sodium metabisulfite). Upon completion of an experiment, rats were killed and histological analysis of each brain was performed to verify the locations of the probes.

Perfusate samples were analyzed by HPLC with electrochemical detection. The HPLC consisted of a Waters pump (model 510), a WISP autosampler (model 712), a Phase Separation Spherisorb C-18 column (S3 ODS2; 10 cm $\times$ 4.6 mm) and a Waters detector (model 464). The mobile phase consisted of 6.9 g/l sodium monobasic phosphate, 450 mg/l heptane sulfonic acid, 80 mg/l disodium EDTA, and 110 ml/l methanol; the solution was adjusted with HCl to pH 3.7 and was pumped at a rate of 1.2 ml/min. Chromatograms were processed using Hewlett–Packard HPLC 2D Chem Station software.

Fig. 1 shows the effects of noribogaine on morphine and cocaine self-administration and on bar-pressing for water. Acutely (Day 1), noribogaine decreased morphine and cocaine intake as well as responding for water (ANOVA, $P < 0.01$, in each case). However, while responding for water returned to baseline a day later, noribogaine continued to depress morphine and cocaine intake for at least a day afterwards. In both of the latter cases, a group $\times$ days interaction was significant ($P < 0.05$ in a two-way ANOVA for days 2–7), and paired t -tests with baseline values were significant ($P < 0.05$) for day 2 in both of the noribogaine treatment groups. The extent of these aftereffects (one or more days later) on drug self-administration varied from rat to rat; responses beyond a day later (Day 2) ranged from no further effect to a prolonged depression of morphine or cocaine intake for up to 2 weeks.

The Med Associates interface and software provided cumulative and event records of responding for each self-administration test session. For both morphine and cocaine, normal patterns of responding were characterized by an initial burst of drug intake at the beginning of each session followed by regularly spaced responding thereafter. Two kinds of noribogaine-induced effects, very similar to those produced by ibogaine and other *iboga* alkaloids [2], were clearly apparent. Acutely, on the day of administration, noribogaine suppressed responding almost entirely in most animals. In contrast, the prolonged aftereffects of noribogaine on morphine and cocaine intake were charac-

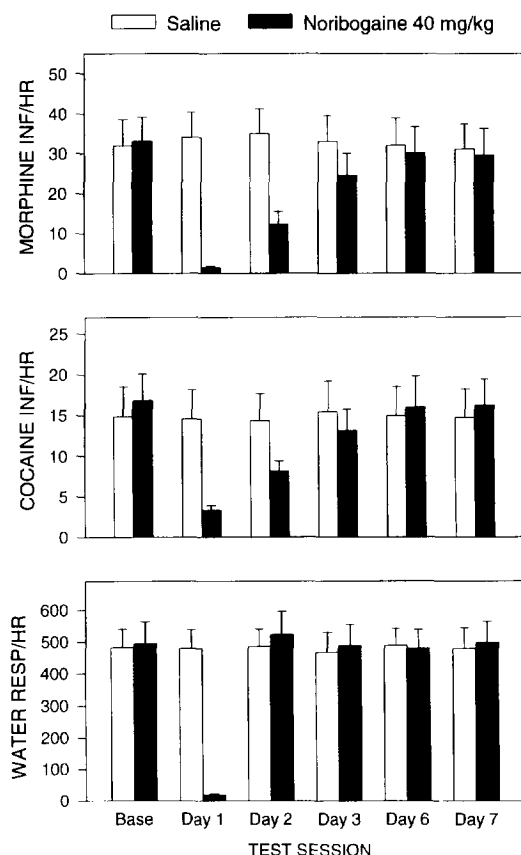


Fig. 1. Effects of noribogaine (40 mg/kg) on morphine and cocaine self-administration and on bar-press responding for water. Each data point is the mean ($\pm$ S.E.) from 5 to 6 rats. 'Base' refers to the baseline rate of responding, calculated as the average for the three sessions preceding drug or saline treatment. There were significant effects on Day 1 in all cases and on both Days 1 and 2 in rats self-administering morphine or cocaine (ANOVA and *t*-tests, $P < 0.05$ – 0.01).

terized by quite normal patterns of responding; that is, although responding was depressed, the effects were distributed uniformly throughout a test session such that the initial burst in responding was shorter and subsequent responses were more widely spaced than during baseline conditions.

Fig. 2 shows the effect of noribogaine on morphine-induced locomotor stimulation. Noribogaine significantly reduced the effect of morphine during the first hour of testing (ANOVA, significant treatment $\times$ time interaction, $P < 0.009$; Newman-Keuls, first hour, $P < 0.05$).

Fig. 3 shows the acute effects of noribogaine on extracellular levels of dopamine in the nucleus accumbens (NAC) and striatum. Noribogaine significantly (ANOVA) decreased DA levels in both regions ($P < 0.02$ and 0.05 in NAC and striatum, respectively). There were also transient but significant (ANOVA and Newman-Keuls) increases (20–40%; data not shown) in striatal DOPAC (20–40 min) and in both NAC and striatal HVA (40–80 min; $P < 0.04$ – 0.001).

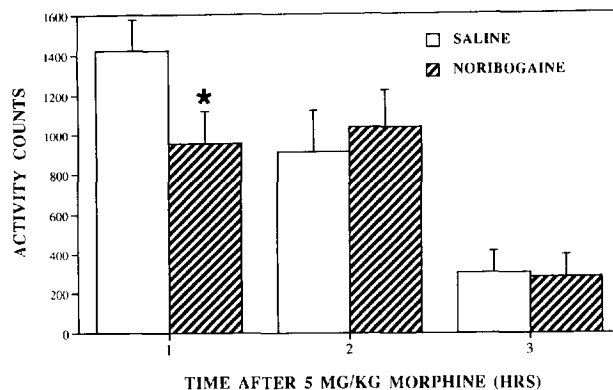


Fig. 2. Effects of morphine (5 mg/kg) on locomotor activity of rats pretreated 19 h earlier with either noribogaine (40 mg/kg) or saline. Each data point is the mean ($\pm$ S.E.) from 8 rats. There was a significant difference between groups during the first hour (Newman-Keuls, $P < 0.05$).

The effects of noribogaine bear a striking resemblance to the effects previously observed with ibogaine [2,4,5,9]. Both ibogaine and noribogaine depressed morphine and cocaine self-administration for prolonged and variable periods of time, both antagonized the locomotor stimulant effect of morphine, and both decreased extracellular levels of DA in NAC and striatum; even the noribogaine-induced increases in DA metabolites were similar to previous results with ibogaine [5].

The similarity of ibogaine's and noribogaine's effects raises the issue of the extent to which ibogaine's effects are mediated by conversion to noribogaine. If noribogaine were totally responsible for ibogaine's effects, it might be expected that noribogaine would be much more potent than ibogaine, i.e., in order to account for ibogaine's

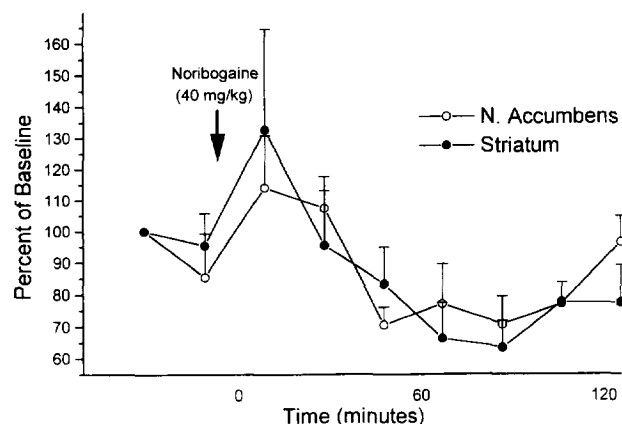


Fig. 3. Time course of extracellular dopamine in the nucleus accumbens and striatum after administration of noribogaine (40 mg/kg, $n = 6$). Samples were collected at 20-min intervals. Data are expressed as a percent ($\pm$ S.E.) of baseline dialysate values. There were significant decreases in dopamine in both regions (ANOVA, $P < 0.02$ – 0.05).

effects at a time (e.g., more than 24 h after administration) when ibogaine itself is no longer detectable in brain and noribogaine is present at modest concentrations [6]. Systemically, based on the present results, this does not appear to be the case (i.e. the effects of noribogaine were no greater than those of the same dose of ibogaine); and, in fact, preliminary data with lower doses suggest that noribogaine may be slightly less potent than ibogaine. However, ibogaine is much more lipid soluble than noribogaine [12], the former entering the brain more readily than the latter, so it is possible that noribogaine is considerably more potent than ibogaine at critical sites of action; indeed, noribogaine's affinities for kappa opioid receptors [9] and serotonin transporter sites [7] are considerably greater (fourfold and tenfold, respectively) than those of ibogaine. It should also be noted that, at 40 mg/kg, ibogaine elicits very obvious whole body tremors (e.g. [2]) whereas, in the present study, noribogaine, at the same dosage, elicited no apparent tremors, consistent with previous observations of others in mice [12]. It appears then that noribogaine does not mediate all of ibogaine's effects but may rather selectively mediate those putative anti-addictive effects that persist for prolonged periods of time. We have previously observed that ibogaine is sequestered in fat, and have suggested that ibogaine's long-term effects are mediated by slow release from fat tissue and subsequent conversion to noribogaine [3]. The present data are certainly consistent with this hypothesis.

Acknowledgements

This research was supported by NIDA Grant DA-03817. We thank J. Raucci for technical assistance.

References

- [1] Cappendijk, S.L.T. and Dzoljic, M.R., Inhibitory effects of ibogaine on cocaine self-administration in rats, *Eur. J. Pharmacol.*, 241 (1993) 261–265.
- [2] Glick, S.D., Kuehne, M.E., Raucci, J., Wilson, T.E., Larson, T.D., Keller, R.W. and Carlson, J.N., Effects of *iboga* alkaloids on morphine and cocaine self-administration in rats: relationship to tremorigenic effects and to effects on dopamine release in nucleus accumbens and striatum, *Brain Res.*, 657 (1994) 14–22.
- [3] Glick, S.D., Maisonneuve, I.M., Pearl, S.M., Deibel, C.R., Gallagher, C.A. and Hough, L.B., Mechanism of action of ibogaine: role of kappa opioid effects, *NIDA Res. Monogr.*, in press.
- [4] Glick, S.D., Rossman, K., Steindorf, S., Maisonneuve, I.M. and Carlson, J.N., Effects and aftereffects of ibogaine on morphine self-administration in rats, *Eur. J. Pharmacol.*, 195 (1991) 341–345.
- [5] Maisonneuve, I.M., Keller, R.W. and Glick, S.D., Interactions between ibogaine, a potential antiaddictive agent, and morphine: an *in vivo* microdialysis study, *Eur. J. Pharmacol.*, 199 (1991) 35–42.
- [6] Mash, D.C., Staley, J.K., Baumann, M.H., Rothman, R.B. and Hearn, W.L., Identification of a primary metabolite of ibogaine that targets serotonin transporters and elevates serotonin, *Life Sci.*, 57 (1995) PL 45–50.
- [7] Mash, D.C., Staley, J.K., Pablo, J.P., Holohean, A.M., Hackman, J.C. and Davidoff, R.A., Properties of ibogaine and its principal metabolite (12-hydroxyibogamine) at the MK-801 binding site of the NMDA receptor complex, *Neurosci. Lett.*, 192 (1995) 53–56.
- [8] Paxinos, G. and Watson, C., *The Rat Brain in Stereotaxic Coordinates*, Academic Press, Orlando, FL, 1986.
- [9] Pearl, S.M., Herrick-Davis, K., Teitler, M. and Glick, S.D., Radioligand binding study of noribogaine, a likely metabolite of ibogaine, *Brain Res.*, 675 (1995) 342–344.
- [10] Pearl, S.M., Johnson, D.W. and Glick, S.D., Prior morphine exposure enhances ibogaine antagonism of morphine-induced locomotor stimulation, *Psychopharmacology*, in press.
- [11] Weeks, J.R., Long-term intravenous infusion. In R.D. Myers (Ed.), *Methods in Psychobiology*, Vol. 2, Academic Press, New York, 1972, pp. 155–168.
- [12] Zetler, G., Singbartl, G. and Schlosser, L., Cerebral pharmacokinetics of tremor-producing harmala and iboga alkaloids, *Pharmacology*, 7 (1972) 237–248.